Doc. Ref: EMA/383877/2010

WITHDRAWAL ASSESSMENT REPORT

FOR

Docetaxel Mylan
10 mg/ml, powder and solvent for solution for infusion

International Nonproprietary Name:

Docetaxel anhydrous

Procedure No. EMEA/H/C /1193

Day 120 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Docetaxel Mylan, in the combination treatment of gastric adenocarcinoma, breast, prostate, head and neck cancer, and in monotherapy for breast cancer and non-small cell lung cancer in patients with locally advanced or metastatic tumours after failure of prior chemotherapy, is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

II. EXECUTIVE SUMMARY

Introduction

This dossier concerns an authorisation application for the generic product Docetaxel Mylan 10 mg/mL solution for infusion, which is presented in a powder form with a matching solvent. The Applicant claims that the product is essentially similar to the reference product, Taxotere 20 mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion, which was granted EU marketing authorization on 27 November 1995. Therefore the application was filed under Article 10.3 of Directive 2001/83/EC (a hybrid application).

The active ingredient docetaxel is an anti-neoplastic agent and a semi-synthetic analogue of paclitaxel. It's chemical name is (2R,3S)-*N*carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13 ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel's primary mechanism of action is the promotion of tubulin assembly and the inhibition of depolymerisation by binding on the β-subunit of tubulin. Due to the fact that it has a higher affinity than paclitaxel for the same binding sites on the microtubuli its potential as a tubulin assembly promoter and microtubule stabilizer is markedly greater than the latter product. Docetaxel has shown activity in a number of solid tumours and is licensed in the following cancers: breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma & head and neck cancer.

II.1 Quality

Drug Substance

The drug substance, *i.e.* docetaxel anhydrous, is a semi-synthetic analogue of paclitaxel, with the chemically name of (2R,3S)-*N*carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13 ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.
Contrary to the reference medicinal product, in which **docetaxel trihydrate** is used as the drug substance, the submitted dossier describes **docetaxel anhydrous** used in the composition of the drug product.
The molecule possesses 11 asymmetric carbon atoms, resulting in a considerable number of potential stereoisomers. Only one isomer as given in the chemical name is defined as the drug substance. This configuration is the one that appears in natural taxanes as paclitaxel. One other diastereoisomer, *i.e.* 7-epidocetaxel, is a potential synthesis but also degradation impurity.
Recently, the trihydrate has been introduced in the Ph. Eur. (6.6), coming into force from January 2010.

The drug substance could be supplied by two manufacturers, both using the ASMF procedure.

- First manufacturer: The manufacture part is satisfactorily described but questions on clarification are asked.
  The elucidation of the structure of the drug substance is adequately discussed, but some information on peak assignment is missing. It has been demonstrated that the same polymorph is consistently formed. An overview of impurities is given, however, the data proving the absence of a chemical element should be submitted.
  The control of the drug substance is acceptable, provided some questions on tightening of acceptance limits would be addressed appropriately. In addition, reference standards are to be defined more appropriately.
  The re-test period has been determined 12 months using a storage condition "20-25°C", which is not according current guidelines. This should be adapted.
- The drug substance from the second manufacturer has already been assessed in several DCP procedures, of which one has been finalised at least regarding the drug substance. No thorough assessment has been made anymore. The questions are limited in asking a complete update of the ASMF taking into consideration the issues from the finalised procedure and some additional questions from a still on-going other DCP procedure.

- Elucidation of structure and discussion of impurities is satisfactorily. Different polymorphs have been obtained, of which 1 anhydrous polymorph is consistently formed.
  Regarding the specification, it has been asked to align the limits with the similar Ph. Eur. monograph for the trihydrate (coming into force on January 2010).
  The retest period is 12 months at 5°C±3°C, protected from light.

Drug Product

The powder for solution for infusion is a lyophilisate, available in three dosage strengths corresponding to 20 mg, 80 mg and 200 mg of anhydrous docetaxel.
The dedicated solvent contains a polyethylene glycol stearate and ethanol in water for injections, supplied as 2 ml, 8 ml and 20 ml solution.
The final concentration after dissolution in the solvent is 10 mg / ml.
The infusion could be prepared into an infusion bag or bottle of either 0.9 % sodium chloride solution or 5% glucose solution to produce a final concentration of 0.3 to 0.74 mg/ml.

With regard to the pharmaceutical development, **a major objection** has been formulated. Given that the drug substance is not very soluble in aqueous solutions, a tensioactive agent is used for solubilising the drug substance as micelles in the solution / infusion solution. However, the micelle-forming system is different from that of the reference product (a polyethylene glycol stearate *vs*. polysorbate). From a bioequivalence point of view, micelle solutions for IV administration may be potentially regarded as "complex" solutions and therefore do not directly qualify for a biowaiver. It should be shown that the quality / physicochemical properties, safety and efficacy are comparable with the reference product, as both types of micelles cannot be assumed to be clinically equivalent due to the known differences in safety profile of these two surfactants and their different potential to affect the kinetics of co-administered drugs. Only a comparison of the particle size of the micelles in a solution mimicking blood plasma has been presented.

Concerning manufacturing, some minor issues are pending.
With regard to the specification, it is asked to tighten some acceptance limits.

Similarly to the concerned section of the drug substance, the reference standard should be better characterised and additional information is asked.
The proposed shelf-life of 12 months without any temperature storage condition, for both the powder and the solvent, is acceptable. In-use times for the reconstituted solution and the infusion have been determined. A conservative strategy is applied by limiting the proposed in-use times more in the SPC than it has been demonstrated in the dossier.

II.2 Non-Clinical

The application is being made in accordance with Article 10.3 of Directive 2001/83/EC (i.e. a hybrid application) and is based on a claim of 'essential similarity' with Taxotere 20 mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion. In accordance with the requirements for such an application, this MAA does not include any nonclinical studies that have been conducted by the Applicant. Taxotere, the reference product, contains Polysorbate and ethanol, while Docetaxel Mylan contains a polyethylene glycol stearate and ethanol. Both Polysorbate and the polyethylene glycol stearate are surfactants.

<u>Docetaxel</u>

Pharmacodynamic, pharmacokinetic and toxicological properties of Docetaxel are well known. As Docetaxel is a widely used, well-known active substance, the Applicant has not provided additional studies. The provided overview based on literature review is, considered appropriate.

Since Docetaxel Mylan has the same active substance as Taxotere, it is expected that environmental exposure will not be significantly altered and therefore the absence of an environmental risk assessment by the Applicant is considered acceptable.

<u>Polyethylene glycol stearate</u>

As part of the safety package, safety pharmacology studies (non-GLP) were conducted by the Applicant on the polyethylene glycol stearate. It was well tolerated at the oral as well as intravenous doses tested for any effects on the central nervous, respiratory and cardiovascular system in mice and dogs. Thus, safety pharmacology studies demonstrated that this ingredient has no potential to adversely affect the safety of a drug product. As expected, the reference compound Cremophor EL produced a pronounced hypotensive reaction of the delayed type in the dog. On the contrary, only a slight and very brief decrease in blood pressure was noted in anesthetized dogs, which had received 115 mg/kg body weight polyethylene glycol stearate *via* the intravenous route.

In conclusion, this ingredient demonstrated superior safety, compared to the well-established solubilizer Cremophor EL, for parenteral dosage forms. However, it can not be fully excluded that intravenous polyethylene glycol stearate might exert slight hypotension in sensitive species.

Polyethylene glycol stearate will be administered via intravenous route. There are no non-clinical pharmacokinetic data to support i.v. administration of this excipient. As the polyethylene glycol stearate has never been used within the EU as an excipient for a human medicinal product intended for intravenous administration, this is considered a deficiency.

Comparative pharmacokinetic (and pharmacodynamic) data on the final formulation of Docetaxel Mylan, i.e. docetaxel in the presence of the new excipient, are totally lacking. This is considered unacceptable taking into account that polysorbate (which is used in the formulation of Taxotere) influences the disposition of intravenously administered docetaxel, with as overall effect a highly increased systemic drug exposure (increased unbound fraction up to 50%) and thus alteration in the pharmacodynamic characteristics of the solubilised drug (ten Tije et al 2003). As stated in Directive 2001/83/EC as amended, Article 10.3 *"In cases where the medicinal product does not fall within the definition of a generic medicinal product … or in cases of changes … in pharmaceutical form …, the results of the appropriate pre-clinical tests or clinical trials shall be provided"*.

Single dose toxicity studies with the polyethylene glycol stearate have been conducted in mice, rats, dogs and rabbits. This ingredient showed practically no acute ingestion hazard in rats and mice. For both species, the oral LD50 was above 20,000 mg/kg body weight. After single acute intraperitoneal and intravenous administration, the polyethylene glycol stearate is characterized by a low toxicity potential (LD50 ranged between 1,000 - 8,740 mg/kg body weight). In Beagle dogs, this ingredient caused no deaths and therefore the intravenous LD50 was above 3,160 mg/kg body weight. Only in this species symptoms indicative for a spontaneous histamine release were noted in a dose-dependent severity but all symptoms disappeared within 2 to 4 hours.

Repeated intravenous injections of the polyethylene glycol stearate to rats for 3 months and dogs for 4 weeks led to species specific findings, which are discussed below. After repeated application of this ingredient to rats, no signs of systemic toxicity, except for RES storage effects, were observed at intravenous dose levels of up to 750 mg/kg body weight/day applied daily for up to 3 months (> 90 consecutive injections). As reversibility was observed only at the dose level of 75 mg/kg/day (Study Number 53 K), the NOAEL is set at 75 mg/kg/day, the NOEL at 25 mg/kg/day. General organ function has not been investigated as neither clinical chemistry nor haematology was studied. A safety margin of about 5-fold (on the basis of allometric scaled dose) exists as compared to the maximum human therapeutic dose which would entail an exposure to 4.4 mg of the polyethylene glycol stearate.

Reference is made to Study Number 87H/82 as a 3-month repeat dose toxicity study of the polyethylene glycol stearate in rats. However, as this study mentions Cremophor HS15 as test substance, it is not clear whether either Cremophor was used or the polyethylene glycol stearate. This should be clarified.

The RES storage effect observed in the 3-month rat study was further investigated in the framework of subsequent 2- and 4-week studies, employing specific staining methods. Lipid deposits in hepatic and splenic cells of the RES, as well as agglomeration of cells containing lipid drops in the liver were seen. Reversibility at lower dose levels was shown and at 25 mg/kg body weight/day none of these findings were detectable within the 4-week study. These lipid granules-containing cells of the RES are regarded as transient storage phenomena within the physiological processes of elimination of foreign substances. While the finding is considered to be of no toxicological concern, general organ function has not been investigated as neither clinical chemistry nor haematology was studied. The NOEL for intravenous administration was established at 25 mg/kg body weight/day.

In contrast, dogs showed clinical findings indicative of an anaphylactoid reaction with a release of histamine after single and repeated intravenous application of the polyethylene glycol stearate (between 50 and 200 mg/kg body weight/day). This finding occurred even after the first injection, an immune mediated allergic background is therefore excluded. In all cases, the symptoms were short and lasted in the GLP conform 4-week study even at the highest dose level of 100 mg/kg body weight/day for minutes only and were totally reversible. Plasma histamine levels were investigated, but showed great variation and no clear correlation between histamine level and intensity and duration of the anaphylactoid reactions could be established. A dose level that caused neither a clinical finding nor elevated histamine levels was established at 25 mg/kg body weight/day (NOAEL). In this dog study, specific staining procedures in histology revealed no indications of lipid storage in the cells of the RES or agglomeration of cells containing lipid drops in the liver and hematology, clinical chemistry, urinalysis and pathology revealed no signs of systemic toxicity.

A safety margin of about 14-fold (on the basis of allometric scaled dose) exists as compared to the maximum human therapeutic dose which would entail an exposure to 4.4 mg of the polyethylene glycol stearate.

Toxicity data on the final formulation of Docetaxel Mylan, i.e. docetaxel in the presence of the new excipient, are totally lacking. Comparison has been made only between the polyethylene glycol stearate and Cremophor EL-only and these data indicate that the new excipient is about 20-fold less potent to induce histamine release in the dog. There is no comparison with polysorbate, the surfactant used in the formulation of Taxotere. Moreover, no consideration is given to taxane-induced hypersensitivity reactions and the possible additive effects with the polyethylene glycol stearate. Consequently, a toxicity study with the final formulation of Docetaxel Mylan, in the most sensitive and relevant species, is required to claim comparable toxicity between the present formulation and the one of the originator and necessary to provide an understanding of the toxicological profile of docetaxel in presence of this new surfactant in the final formulation. The influence of these groups of excipients on the pharmacokinetic properties of docetaxel makes it of importance to study these interactions in the non-clinical setting. **This is a major deficiency.**

The polyethylene glycol stearate did not show any genotoxic effects in a *Salmonella typhimurium* reverse mutation assay (Ames test), in a gene mutation test in V79 cells, in a cytogenetic assay in the same cell type and in the mouse micronucleus test.

Two studies with intravenous application were conducted concerning reproductive and developmental toxicity. The combined embryotoxicity and pre- and postnatal reproduction toxicity study in rats revealed no substance-related influence on the prenatal development of the embryo or fetus, the postnatal growth and survival of pups and the reproductive parameters up to the highest tested dosage of 464 mg/kg body weight/day. There were no signs of teratogenicity in rats and the NOEL for dams and reproductive toxicity was above 464 mg/kg body weight/day. A safety margin of about 104-fold (on the basis of allometric scaled dose) exists as compared to the maximum human therapeutic dose which would entail an exposure to 4.4 mg of the polyethylene glycol stearate.

The rabbit study did also show no teratogenic potential, however a high intravenous dose of 464 mg/kg body weight/day revealed indications for a possible embryo- / fetotoxic effect at the top dose. In rabbits, the NOEL is therefore 464 mg/kg for dams and teratogenic effects and 215 mg/kg for fetotoxicity. A safety margin of about 97- and 210-fold (on the basis of allometric scaled dose) exists respectively for fetal effects and maternal toxicity as compared to the maximum human therapeutic dose which would entail an exposure to 4.4 mg of the polyethylene glycol stearate.

No local intolerance or irritation at the application site after intravenous application could be observed histopathologically. The evaluation of irritation studies led to the conclusion that the polyethylene glycol stearate is slightly irritating to the intact skin and not irritating to the eyes of rabbits. There are no local tolerance data on the final formulation of Docetaxel Mylan.

Positive skin reaction observed in the Maximization Test after challenging with undiluted the polyethylene glycol stearate can be contributed to the skin irritating potential of the polyethylene glycol stearate in Guinea pigs, as described in the Open Epicutaneous Test. However, it cannot be ruled out that a hypersensitive human subpopulation may respond positive to skin sensitization.

The hemolytic activity of the polyethylene glycol stearate was tested over a range of 0.001 to 100 mg/mL by colorimetric measurement of the amount of hemoglobin released by erythrocytes from rabbit blood. No hemolytic activity could be observed under the test conditions for all concentrations.

Conclusion

Toxicological and pharmacological aspects of this application are therefore limited to those known for the drug substance, ethanol and the polyethylene glycol stearate.

From a non-clinical point of view, a MA cannot be granted as 2 major objections have been formulated pertaining to following major deficiencies:

- Comparative pharmacokinetic (and pharmacodynamic) data on the final formulation of Docetaxel Mylan, i.e. docetaxel in the presence of the new excipient are totally lacking. This is considered unacceptable taking into account that polysorbate (which is used in the formulation of Taxotere) influences the disposition of intravenously administered docetaxel, with as overall effect a highly increased systemic drug exposure (increased unbound fraction up to 50%) and thus alteration in the pharmacodynamic characteristics of the solubilised drug (ten Tije et al 2003).

As stated in Directive 2001/83/EC as amended, Article 10.3 *"In cases where the medicinal product does not fall within the definition of a generic medicinal product … or in cases of changes … in pharmaceutical form …, the results of the appropriate pre-clinical tests or clinical trials shall be provided."*.
Consequently the lack of non-clinical comparative pharmacokinetic and pharmacodynamic studies on the final formulation of Docetaxel Mylan are considered a major deficiency if clinical bioequivalence is not documented.
If comparability at the quality and non-clinical levels is adequately demonstrated, bioequivalence studies are not needed (as per the CHMP note CPMP/EWP/QWP/1401/98 Rev 1). If, however, comparability of Docetaxel Mylan 10 mg/ml and Taxotere 20 mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion is not demonstrated by the data on pharmaceutical quality and non-clinical investigations, Docetaxel Mylan 10 mg/ml should be considered as essentially different from the reference product, Taxotere, and therefore a stand alone module 5 should be required. Such a stand alone application has not currently been submitted.

- The Applicant did not provide toxicity data on the final formulation of Docetaxel Mylan, i.e. docetaxel in the presence of the new excipient. Comparative toxicity data have been provided for the polyethylene glycol stearate only and Cremophor EL-only and these data indicate that the polyethylene glycol stearate is about 20-fold less potent to induce histamine release in the dog. There is no comparison with polysorbate, the surfactant used in the formulation of Taxotere. Moreover, no consideration is given to taxane-induced hypersensitivity reactions and possible additive effects with the polyethylene glycol stearate. Consequently, a toxicity study with the final formulation of Docetaxel Mylan, in the most sensitive and relevant species, is required to claim comparable toxicity between the present formulation and the one of the originator and necessary to provide an understanding of the toxicological profile of docetaxel in presence of this new surfactant in the final formulation. The influence of these groups of excipients on the pharmacokinetic properties of docetaxel makes it of importance to study these interactions in the non-clinical setting.

In addition the identified other concerns need to be adequately addressed.

II.3 Clinical

This clinical assessment concerns the hybrid generic application, filed under Article 10.3 of Directive 2001/83/EC, for the product Docetaxel Mylan by Mylan S.A.S. The product is claimed to be 'essentially similar' to the reference product, Taxotere 20 mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion. The active ingredient, docetaxel, is a semi-synthetic analogue of paclitaxel which promotes tubulin assembly and inhibits depolymerisation, thereby preventing mitotic division by disrupting the dynamics of the microtubular network which ultimately leads to apoptosis of the cell.

Indications and posology are identical to the reference product. Likewise, the SmPC is an almost ad verbatim copy of the reference product's SmPC, except for the inherent particulars. During this application, no new efficacy or safety studies were undertaken by the Applicant. Instead, they relied solely on the scientific literature available on the usage of docetaxel in the indicated treatments. Said literature does indeed support the safety and efficacy of the (well-known) active ingredient claims in the proposed indications. However, it is important to note that the articles used do not refer specifically to the Docetaxel Mylan composition of the product.

In fact, Docetaxel Mylan is not 100% identical to the reference product (hence the hybrid application). As taxanes are poorly soluble, a surfactant is often used in order to form taxane-loaded micelles, which are then able to deliver the active ingredient to the target site. Taxotere uses polysorbate towards this goal, whereas Docetaxel Mylan uses a polyethylene glycol stearate. Despite the fact that these two excipients are different, the Applicant claims that no bioequivalence, biopharmaceutical or PK studies need to be undertaken.

For this assumption they base themselves on the CHMP note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) states that "*bioequivalence studies are not required (for parental solutions) if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. Moreover, the excipients, pH and osmolality have to be the same or, at least, comparable, and should not interact with the drug substance (e.g. complex formation)*". Since the comparability of polysorbate and the polyethylene glycol stearate has supposedly been proven in the quality and non-clinical dossiers by a study done by the manufacturer of the active substance, the Applicant claims that they are exempt from undertaking any bioequivalence study.

However, the CHMP has expressed serious doubts concerning the manufacturer study's capability in establishing similarity between the effects of polysorbate and the polyethylene glycol stearate (see their respective reports). Furthermore, the Applicant did not demonstrate how the polyethylene glycol stearate will influence protein binding and clearance of the active component, even though it has been empirically proven that polysorbate does have influences these factors. Furthermore, in 2003 a review was published (Tije *et al.*) in which surfactants and the micellar structures they created were shown to influence the disposition of solubilised drugs administered intravenously, leading to a higher systemic drug exposure and decreased clearance which in turn led to changes in the pharmacodynamic drug characteristics. When one combines these findings with the fact that there is no conclusive proof of equivalence of the polyethylene glycol stearate with polysorbate, the fact that the Applicant did not do any bioequivalence or PK testing cannot be endorsed.

Thus the claims of having no need for such testing are not supported, at least for as long as similarity between the surfactants of the product and the reference drug have not been sufficiently proven from a quality and non-clinical viewpoint.

Secondly, as the combination of docetaxel and the polyethylene glycol stearate is rather novel, the lack of specific clinical efficacy and safety studies can equally not be endorsed. The PK and efficacy profiles of docetaxel may be in fact different in this combination of active ingredient and excipient, as surfactants are known to influence the disposition of intravenously administered solubilised drugs. Likewise, as the polyethylene glycol stearate is a novel excipient for use in infusions, there is currently no information known about possible safety issues arising from it's use as such (or in combination with docetaxel). Clinical safety studies are therefore needed to look for potential safety signals such as hypersensitivity; anaphylactic allergic reactions, etcetera.

A final potential issue which arose during the assessment of this dossier was the fact that Docetaxel Mylan contains a higher volume of ethanol, needed for the solubility of the surfactant, compared to the reference product. However, the Applicant is right in pointing out that Paclitaxel, another taxane drug, contains an even greater amount of ethanol and has never been known to show any worrisome problems related to this fact. Coupled with the fact that the Applicant included appropriate warnings in the SPC, the CHMP feels that this issue is actually of no concern at this point.

In conclusion, although no efficacy or safety concerns were raised by the literature reviews and despite the fact that the indications, posology and SmPC contents are an ad verbatim copy of the reference product's (except for the inherent characteristics of each product), the clinical part of the dossier cannot be endorsed as of yet. The Company should either provide compelling quality and non-clinical evidence of the polyethylene glycol stearate's similarity to polysorbate in its function of a surfactant, or they should conduct clinical bioequivalence and PK studies. Furthermore, clinical safety and efficacy studies specifically targeted towards the combination of docetaxel and the polyethylene glycol stearate are necessary as the reviewed literature did never address this particular novel combination.

Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The CHMP considers that the justification for the absence of a Risk Management Plan is not satisfactory.
Docetaxel Mylan uses a polyethylene glycol stearate as excipient-surfactant. The combination of docetaxel and this ingredient is rather novel and its safety is not demonstrated. Furthermore,it has not been used before in an infusion solution in EU.
According to non-clinical and clinical safety conclusions (major objections), (clinical) safety studies are needed to investigate potential safety issues arising from this combination and new route of administration (hypersensitivity, anaphylactic allergic reaction …).

The CHMP requires an EU-RMP for this hybrid generic medicinal product where the changes compared with the reference product suggest different risks.

Comments on compliance with GLP,GMP, GCP

None

Comments on the SPC and Package Leaflet of the generic product

The SmPC is an ad verbatim copy of the Taxotere SmpC, except for those sections which are about the specific pharmaceutical features of the product. The only clinically relevant change made is the addition of a line under section 4.4 which reflects the higher ethanol content of Docetaxel Mylan:

'Since Docetaxel Mylan contains ethanol consideration should be given to possible CNS and other effects.'

This information is ad verbatim equal to the ethanol related warning found in the Paxene (which contains an even higher ethanol content level than Docetaxel Mylan) SmPC.

The Docetaxel Mylan PIL is likewise an ad verbatim copy of the reference product PIL, except for the inherently different specific product characteristics. Due to the higher ethanol content of Docetaxel Mylan, section 2 'Driving and using machines' has been adapted to:

'There is no reason why you cannot continue driving between courses of DOCETAXEL MYLAN but you should remember that this medicine contains some alcohol and it may be unwise to drive immediately after a course of treatment. In all cases, you should not drive if you feel dizzy or are unsure of yourself.'

II.4 Overall conclusion and Benefit Risk assessment

Overall, the MA-application for Docetaxel Mylan in its current form cannot be endorsed.

The active ingredient, docetaxel, is a well-known agent in oncologic medicine and has been extensively characterised on its efficacy and safety profile through the years. As such, no pertaining clinical or non-clinical problems were raised.

However, Docetaxel Mylan uses a different surfactant, used to form drug-loaded micelles, in its composition than the reference product (a polyethylene glycol stearate versus polysorbate respectively). This does however raise serious objections to the fact that the Applicant claims essential similarity between the two drugs as evidenced by their reliance on the CHMP note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) to support the absence of bioequivalence studies.

There are serious problems with this point of view from both a quality and a non-clinical/clinical perspective though.

The CHMP found the micelle-forming system to be different compared to that of the reference product. As micelle solutions for IV administration may be potentially regarded as "complex" solutions, they do not directly qualify for a biowaiver. As both types of micelles cannot be assumed to be clinically equivalent due to the known differences in the safety profiles of these two surfactants and their different potential to affect the kinetics of co-administered drugs, equality of the quality/physicochemical properties, safety and efficacy to the reference product should be specifically demonstrated. However, only a comparison of the particle size of the micelles in a solution mimicking blood plasma has been presented in the dossier.

From a non-clinical point of view comparability of the polyethylene glycol stearate to polysorbate in the role of a surfactant has not been proven as no comparative pharmacokinetic or -dynamic data were provided. As surfactants influence the disposition of intravenously administered docetaxel, resulting in a highly increased systemic drug exposure and thus alteration in the pharmacodynamic characteristics of the solubilised drug (ten Tije et al, 2003), evidence of comparability is vital.

Furthermore, toxicity data on the formulation of Docetaxel Mylan, i.e. docetaxel in the presence of the new excipient was also lacking. The Applicant claimed that hypersensitivity reactions will be less frequent with this new formulation. For this purpose, they provided comparative toxicity data for the polyethylene glycol stearate and Cremophor EL-only and these data indicate that the polyethylene glycol stearate is about 20-fold less potent to induce histamine release in the dog. There is no comparison with polysorbate, the surfactant used in the formulation of Taxotere. Moreover, no consideration is given to taxane-induced hypersensitivity reactions and the possible additive effects with the polyethylene glycol stearate. A toxicity study with the final formulation of Docetaxel Mylan, in the most sensitive and relevant species, is required to claim comparable toxicity between the present formulation and the one of the originator and necessary to provide an understanding of the toxicological profile of docetaxel in presence of this new surfactant in the final formulation.

Finally, from a clinical perspective, problems arose from the fact that comparability of the compositions was not proven in the quality and non-clinical parts of the dossier. This basically means that the CHMP note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) is not valid for this application. Thus the Applicant will have to prove essential similarity with the reference product at the quality and non-clinical level or provide a full stand-alone module 5.

The lack of specific clinical safety studies cannot be endorsed either. The fact that the use of the polyethylene glycol stearate as a surfactant in IV infusions is rather novel needs to be taken into account, as no data on hypersensitivity/allergy in humans when used in this way are available to date. Furthermore, docetaxel in itself is known to induce hypersensitive reactions, thus leaving a possible danger of synergistic effects.

Furthermore, animal hypersensitivity/allergy models cannot be easily extrapolated to humans, thus making studies looking for, among other things, signs of possible hypersensitivity or (anaphylactic) allergy against the product under investigation in humans imperative. At the very least, a study containing 15-20 subjects should be run to investigate these potential issues.

In conclusion, a positive risk/benefit ratio has as of yet not been proven for Docetaxel Mylan. It is thus the CHMP's opinion that, at the time being, the MA cannot (yet) be granted. Either comparability between the product and reference formulations is demonstrated at the quality and non-clinical levels, or a full stand-alone clinical dossier will have to be provided. Furthermore, non-clinical/clinical safety will need to be proven by trials specifically tuned towards the composition of Docetaxel Mylan.